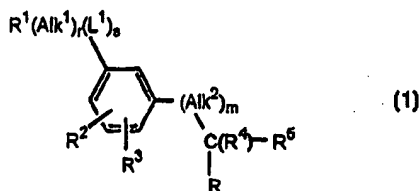




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(71) Applicant (for all designated States except US): CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): HEAD, John, Clifford [GB/GB]; 4 Dorchester Close, Maidenhead, Berkshire SL6 6RX (GB). ARCHIBALD, Sarah, Catherine [GB/GB]; 5 College Glen, Maidenhead, Berkshire SL6 6BL (GB). WARRELOW, Graham, John [GB/GB]; 4 Wieland Road, Oakside, Northwood, Middlesex HA6 3QU (GB). PORTER, John, Robert [GB/GB]; 5 Farm Place, Henton, Chinnor, Oxfordshire OX9 4AD (GB).			
(74) Agents: MERCER, Christopher, Paul et al.; Carpmals & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).			Published With international search report.

(54) Title: PHENYLALANINE DERIVATIVES HAVING VLA-4 ANTAGONISTIC ACTIVITY



(57) Abstract

Phenylalanine derivatives of formula (1) are described, wherein R is a carboxylic acid or a derivative thereof; L¹ is a linker atom or group; and R⁵ is a group -L²(CH₂)_nR⁶ in which L² is a -N(R⁷)CO- or -N(R⁷)CS- group. The compounds are able to inhibit the binding α4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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PHENYLALANINE DERIVATIVES HAVING VLA-4 ANTAGONISTIC ACTIVITY

5 This invention relates to a series of phenylalanine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

10 Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T. A. *Nature*, 346, 425, (1990); Springer, T. A. *Cell* 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

15 The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At
20 least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. *Current Topics in Microbiology and Immunology*, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$
25 consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised
30 [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of
35 leukocyte integrins is not expressed [Marlin, S. D. *et al* *J. Exp. Med.* 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

5 The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al*/ Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al*/ J. Immunol. 157, 4094, (1996)]. A number of
10 monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

15 One particular integrin subgroup of interest involves the $\alpha 4$ chain which can pair with two different beta chains $\beta 1$ and $\beta 7$ [Sonnenberg, A. *ibid*]. The $\alpha 4\beta 1$ pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. $\alpha 4\beta 1$ binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1)
20 frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed
25 that the interaction between $\alpha 4\beta 1$ and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

30 The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like $\alpha 4\beta 1$, binds to VCAM-1 and fibronectin. In addition, $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to
35 mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important at

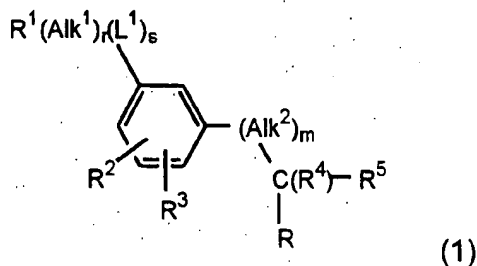
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they
5 bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV,
IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in
VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises a LDT
sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719,
(1996)]. There have been several reports of inhibitors of these interactions
10 being designed from modifications of these short peptide sequences
[Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N.
Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol.
158, 1710, (1997)]. It has also been reported that a short peptide
sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a
15 contact hypersensitivity reaction in a trinitrochlorobenzene sensitised
mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on
leukocytes their inhibition can be expected to be beneficial in a number of
20 immune or inflammatory disease states. However, because of the
ubiquitous distribution and wide range of functions performed by other
members of the integrin family it is very important to be able to identify
selective inhibitors of the alpha 4 subgroup.

25 We have now found a group of compounds which are potent and selective
inhibitors of $\alpha 4$ integrins. Members of the group are able to inhibit $\alpha 4$
integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ at concentrations at which they
generally have no or minimal inhibitory action on α integrins of other
subgroups. The compounds are thus of use in medicine, for example in
30 the prophylaxis and treatment of immune or inflammatory disorders as
described hereinafter.

Thus according to one aspect of the invention we provide a compound of
formula (1)



wherein

- 5 R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
- Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;
- L^1 is a linker atom or group;
- r and s is each zero or an integer 1;
- 10 R^2 and R^3 , which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group;
- Alk^2 is a straight or branched alkylene chain;
- m is zero or an integer 1;
- 15 R^4 is a hydrogen atom or a methyl group;
- R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
- 20 R is a carboxylic acid ($-CO_2H$) or a derivative thereof; and the salts, solvates and hydrates thereof.

It will be appreciated that compounds of formula (1) may have one or more
 25 chiral centres. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless
 30 stated or shown otherwise.

In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include those $-\text{CO}_2\text{Alk}^5$, $-\text{CONH}_2$, $-\text{CONHR}^{12}$ and $-\text{CON}[\text{R}^{12}]_2$ groups described below in relation to the group R^6 .

5

Alk^2 in the compounds of the invention may be for example a straight or branched C_{1-3} alkylene chain. Particular examples include $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$ and $-(\text{CH}_2)_2-$.

- 10 When in the compounds of the invention L^1 is present as a linker atom or group it may be any divalent linking atom or group. Particular examples include $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^8)-$ [where R^8 is a hydrogen atom or an optionally substituted straight or branched alkyl group], $-\text{CON}(\text{R}^8)-$, $-\text{OC}(\text{O})\text{N}(\text{R}^8)-$, $-\text{CSN}(\text{R}^8)-$, $-\text{N}(\text{R}^8)\text{CO}-$,
 15 $-\text{N}(\text{R}^8)\text{C}(\text{O})\text{O}-$, $-\text{N}(\text{R}^8)\text{CS}-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^8)-$, $-\text{N}(\text{R}^8)\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^8)\text{CSN}(\text{R}^8)-$, or $-\text{N}(\text{R}^8)\text{SO}_2\text{N}(\text{R}^8)-$ groups. Where the linker group contains two R^8 substituents, these may be the same or different.

- When Alk^1 and/or R^6 in compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl chains.
- 20

- Heteroaliphatic chains represented by Alk^1 and/or R^6 include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^3 where L^3 is as defined above for L^1 when L^1 is a linker atom or group. Each L^3 atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to an adjoining atom or group.
- 25
- 30

- Particular examples of aliphatic chains represented by Alk^1 and R^6 include optionally substituted $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-(\text{CH}_2)_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_3\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$,
 35 $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-(\text{CH}_2)_4\text{CH}_2-$, $-(\text{CH}_2)_5\text{CH}_2-$, $-\text{CHCH}-$, $-\text{CHCHCH}_2-$, $-\text{CHCHCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CHCHCH}_2-$,

-(CH₂)₂CHCH-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂-, or
-(CH₂)₂CC- chains. Where appropriate each of said chains may be
optionally interrupted by one or two atoms and/or groups L³ to form an
optionally substituted heteroaliphatic chain. Particular examples include
5 optionally substituted -L³CH₂-, -CH₂L³CH₂-, -L³(CH₂)₂-, -CH₂L³(CH₂)₂-,
- (CH₂)₂L³CH₂-, -L³(CH₂)₃- and -(CH₂)₂L³(CH₂)₂- chains.

The optional substituents which may be present on aliphatic or
heteroaliphatic chains represented by Alk¹ and R⁶ include one, two, three
10 or more substituents where each substituent may be the same or different
and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or
iodine atoms, or C₁₋₆alkoxy, e.g. methoxy or ethoxy, thiol, C₁₋₆alkylthio
e.g. methylthio or ethylthio, amino or substituted amino groups.
Substituted amino groups include -NHR⁹ and -N(R⁹)₂ groups where R⁹ is
15 a straight or branched alkyl group. Where two R⁹ groups are present
these may be the same or different. Particular examples of substituted
chains represented by Alk¹ include those specific chains just described
substituted by one, two, or three halogen atoms such as fluorine atoms, for
example chains of the type -CH(CF₃)-, -C(CF₃)₂-, -CH₂CH(CF₃)-,
20 -CH₂C(CF₃)₂-, -CH(CF₃)- and -C(CF₃)₂CH₂.

Optionally substituted cycloaliphatic groups represented by R¹ and/or R⁶
in compounds of the invention include optionally substituted C₃₋₁₀
cycloaliphatic groups. Particular examples include optionally substituted
25 C₃₋₁₀ cycloalkyl, e.g. C₃₋₇ cycloalkyl or C₃₋₁₀ cycloalkenyl, e.g. C₃₋₇
cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by R¹
and/or R⁶ include optionally substituted C₃₋₁₀ heterocycloaliphatic groups.
30 Particular examples include optionally substituted C₃₋₁₀ heterocycloalkyl,
e.g. C₃₋₇ heterocycloalkyl, or C₃₋₁₀ heterocycloalkenyl, e.g. C₃₋₇
heterocycloalkenyl groups, each of said groups containing one, two, three
or four heteroatoms or heteroatom-containing groups L³ as just defined.

35 Optionally substituted polycycloaliphatic groups represented by R¹ and/or
R⁶ include optionally substituted C₇₋₁₀ bi- or tricycloalkyl or C₇₋₁₀ bi- or

tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by R^1 and/or R^6 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^3 atoms or groups.

5

Particular examples of R^1 and R^7 cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolanyl, e.g. 2-imidazolanyl, imidazolidinyl, pyrazolanyl, e.g. 2-pyrazolanyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholanyl, morpholinone, 1,4-dithianyl, thiomorpholanyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

20 The optional substituents which may be present on the R^1 and R^6 cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6} alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6} alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^9$ and $-N(R^9)_2$ groups where R^9 is as defined above. Additionally, when R^6 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^4)_p(Alk^3)_qR^{10}$ in which L^4 is $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)_2-$, $-CON(R^8)-$, $-CSN(R^8)-$, $-SON(R^8)-$ or $SO_2N(R^8)-$; p is zero or an integer 1; Alk^3 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R^{10} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

35

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^3 include those optionally substituted chains described above for Alk^1 .

5 Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocycloaliphatic groups represented by R^{10} include those groups just described for R^1 and R^6 . Optional substituents which may be present on these groups include those described above in relation to Alk^1 aliphatic and heteroaliphatic chains.

10 Optionally substituted aromatic or heteroaromatic groups represented by R^{10} include those aromatic and heteroaromatic groups generally and specifically described below for R^1 and/or R^6 .

15 In the compounds of formula (1), optionally substituted aromatic groups represented by the groups R^1 , R^6 and/or R^{10} include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydro-naphthyl, indanyl or indenyl groups.

20 Optionally substituted heteroaromatic groups, represented by the groups R^1 , R^6 and/or R^{10} in compounds of formula (1) include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for
25 example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered
30 fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl,
35 N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,

1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzo-triazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, 5
benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

10

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by R^1 , R^6 and/or R^{10} include one, two, three or more substituents, each selected from an atom or group R^{11} in which R^{11} is $-R^{11a}$ or $-Alk^4(R^{11a})_m$, where R^{11a} is a halogen atom, or an
15 amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl ($-OH$), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol ($-SH$), substituted thiol, $-COR^{12}$ [where R^{12} is an $-Alk^4(R^{11a})_m$, aryl or heteroaryl group], $-CSR^{12}$, $-SO_3H$, $-SO_2R^{12}$, $-SO_2NH_2$, $-SO_2NHR^{12}$, $SO_2N(R^{12})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{12}$, $-CSNHR^{12}$, $-CON[R^{12}]_2$,
20 $-CSN(R^{12})_2$, $-N(R^8)SO_2R^{12}$, $-N(SO_2R^{12})_2$, $-N(R^8)SO_2NH_2$, $-N(R^8)SO_2NHR^{12}$, $-N(R^8)SO_2N(R^{12})_2$, $-N(R^8)COR^{12}$, $-N(R^8)CON(R^{12})_2$, $-N(R^8)CSN(R^{12})_2$, $-N(R^8)CSR^{12}$, $-N(R^8)C(O)OR^{12}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7} cyclicamino group optionally containing one or more other $-O-$ or $-S-$ atoms or $-N(R^8)-$, $-C(O)-$ or $-C(S)-$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^8)SO_2NHet^1$, $-N(R^8)CONHet^1$, $-N(R^8)CSNHet^1$, $-SO_2N(R^8)Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7} carbocyclic group optionally containing one or more $-O-$ or $-S-$ atoms or $-N(R^8)-$, $-C(O)-$ or $-C(S)-$ groups], $-CON(R^8)Het^2$, $-CSN(R^8)Het^2$, $-N(R^8)CON(R^8)Het^2$, $-N(R^8)CSN(R^8)Het^2$, aryl or
30 heteroaryl group; Alk^4 is a straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three $-O-$ or $-S-$ atoms or $-S(O)_n$ [where n is an integer 1 or 2] or $-N(R^{13})-$ groups [where R^{13} is a hydrogen atom or C_{1-6} alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that
35 when two R^8 or R^{12} groups are present in one of the above substituents, the R^8 or R^{12} groups may be the same or different.

- When in the group $-\text{Alk}^4(\text{R}^{11a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{11a} may be present on any suitable carbon atom in $-\text{Alk}^4$. Where more than one R^{11a} substituent is present these may be the same or different and may be present on the same or different atom in $-\text{Alk}^4$. Clearly, when m is zero and no substituent R^{11a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.
- 10 When R^{11a} is a substituted amino group it may be for example a group $-\text{NHR}^{12}$ [where R^{12} is as defined above] or a group $-\text{N}(\text{R}^{12})_2$ wherein each R^{12} group is the same or different.
- When R^{11a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.
- 15 When R^{11a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-\text{OR}^{12}$ or a $-\text{SR}^{12}$ or $-\text{SC}(=\text{NH})\text{NH}_2$ group respectively.
- 20 Esterified carboxyl groups represented by the group R^{11a} include groups of formula $-\text{CO}_2\text{Alk}^5$ wherein Alk^5 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^5 group include R^{11a} substituents described above.
- 25
- 30
- 35 When Alk^4 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-

butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R⁸)- groups.

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Aryl or heteroaryl groups represented by the groups R^{11a} or R¹² include mono- or bicyclic optionally substituted C₆₋₁₂ aromatic or C₁₋₉ heteroaromatic groups as described above for the group R⁶. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

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When -NHet¹ or -Het² forms part of a substituent R¹¹ each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those substituents described above in relation to Alk¹ chains.

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Particularly useful atoms or groups represented by R¹¹ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrrolyl, furyl, thiazolyl, or thienyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋

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6dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁶ [where Alk⁶ is as defined above], C₁₋₆ alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋₆dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, e.g. ethylaminothiocarbonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g.

methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyl-oxycarbonylaminoethyl, benzothio, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R¹¹ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R¹¹ substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R¹, R⁶ and/or R¹¹.

Alkyl groups represented by the groups R² or R³ in compounds of the invention include for example straight or branched C₁₋₆alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl groups. Alkoxy groups represented by the groups R² or R³ include straight or branched C₁₋₆alkoxy groups such as methoxy or ethoxy groups. Halogen atoms represented by the groups R² or R³ include for example fluorine, chlorine, bromine or iodine atoms. When R² and/or R³ is a haloalkyl or haloalkoxy group it may be for example a haloC₁₋₆alkyl or haloC₁₋₆alkoxy group containing one, two or three halogen atoms selected from fluorine, chlorine, bromine or iodine atoms. Particular examples of groups of this type include -CF₃, -OCF₃, -CCl₃, -OCCl₃, -CHF₂, -OCHF₂, -CHCl₂, -OCHCl₂, -CH₂F, -OCH₂F, -CH₂Cl and -OCH₂Cl groups.

Straight or branched alkyl groups represented by R⁷, R⁸ and/or R⁹ in compounds of the invention include straight or branched C₁₋₆alkyl e.g. C₁₋₃alkyl groups such as methyl or ethyl groups. Each R⁸ group may be optionally substituted, for example by one or more atoms or groups of the types described previously as optional Alk¹ substituents.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include

pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

- 5 Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

- Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

- Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

- 20 Generally in the compounds of the invention the group R is preferably a $-\text{CO}_2\text{H}$ group.

- Alk² in compounds of formula (1) is preferably a $-\text{CH}_2-$ chain and m is preferably an integer 1.

R⁴ in compounds of the invention is preferably a hydrogen atom.

- In general in compounds of formula (1) $-(\text{Alk}^1)_r(\text{L}^1)_s-$ is preferably $-\text{CH}_2\text{O}-$ or $-\text{CON}(\text{R}^8)-$, particularly $-\text{CONH}-$.

- The group R¹ in compounds of formula (1) is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substituted phenyl, pyridyl or pyrimidinyl groups. Where optional substituents are present in these groups they may in particular be selected from one or two fluorine, chlorine, bromine or

iodine atoms, or C₁₋₆alkyl, C₁₋₆alkylamino, C₁₋₆hydroxyalkyl, carboxyC₁₋₆alkyl, C₁₋₆alkylthio, carboxyC₁₋₆alkylthio, C₁₋₆alkoxy, hydroxyC₁₋₆alkoxy, haloC₁₋₆alkyl, haloC₁₋₆alkoxy, C₁₋₆alkylamino, amino (-NH₂), aminoC₁₋₆alkyl, C₁₋₆dialkylamino, C₁₋₆alkylaminoC₁₋₆alkyl, C₁₋₆dialkylaminoC₁₋₆alkyl, aminoC₁₋₆alkoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁶, C₁₋₆alkanoyl, thiol (-SH), thioC₁₋₆alkyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, C₁₋₆alkylaminothiocarbonylamino, C₁₋₆dialkylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, C₁₋₆alkylsulphonylamino, C₁₋₆dialkylsulphonylamino, aminosulphonylamino (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, C₁₋₆alkanoylamino, aminoC₁₋₆alkanoylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, or C₁₋₆alkoxycarbonylamino groups, especially as more particularly defined herein.

Particularly useful classes of compounds according to the invention are those wherein R⁵ is a -NHCOR⁶ or -NHCSR⁶ group.

In general, R⁶ in the group -L²(CH₂)_tR⁶ may especially be an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C₅₋₇heterocycloaliphatic, especially optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C₅₋₇heteroaromatic, especially optionally substituted pyridyl groups. Optional substituents on these groups include in particular R¹¹ atoms or groups where the group is an aromatic or heteroaromatic group and -(L⁴)_p(Alk³)_qR¹⁰ groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group. Particularly useful -(L⁴)_p(Alk³)_qR¹⁰ groups include those in which L³ is a -CO- group. Alk³ in these groups is preferably

present (i.e. q is preferably an integer 1) and in particular is a -CH₂-chain. Compounds of this type in which R¹⁰ is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridinyl or imidazolyl group are particularly preferred.

5

Particularly useful compounds according to the invention include:

N-Acetyl-*D*-thioprolin-3-[(2,6-dichloroisonicotinoyl)amino]-*DL*-phenylalanine;

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N-Acetyl-*D*-thioprolin-3-[(4-methoxyphenylacetyl)amino]-*DL*-phenylalanine;

N-Acetyl-*D*-thioprolin-3-[(2,6-dichlorophenylacetyl)amino]-*DL*-phenylalanine;

2-Chloronicotinoyl-(*O*-2,6-dichlorobenzyl)-*DL*-*m*-tyrosin;

and the salts, solvates and hydrates thereof.

15

Compounds according to the invention are potent and selective inhibitors of α 4 integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

20

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role. The invention extends to such uses and to the use of the compounds for preparing a medicament for treating these diseases and disorders. Particular diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

30

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

35

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

- 5 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline
10 cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or
15 suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer
20 salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

- 25 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

- The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations
30 for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively,
35 the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

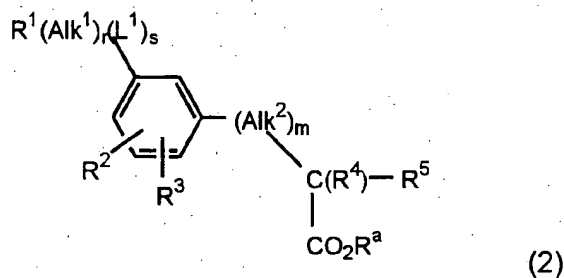
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R, R¹-R⁵, L¹, Alk¹, Alk², m, r and s when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired

in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

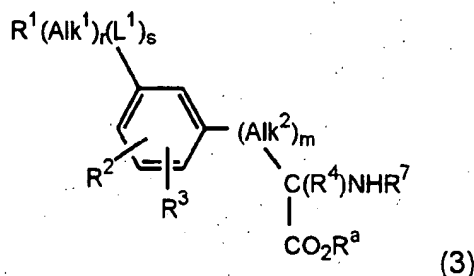
Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-\text{CO}_2\text{H}$ group may be obtained by hydrolysis of an ester of formula (2):



where R^a is an alkyl group, for example a C_{1-6} alkyl group such as a methyl or ethyl group.

The hydrolysis may be performed using either an acid or a base depending on the nature of R^a , for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (2) in which R^5 is a $-\text{N}(\text{R}^7)\text{CO}(\text{CH}_2)_t\text{R}^6$ group may be prepared by coupling an amine of formula (3):



or a salt thereof with an acid $R^6(CH_2)_tCO_2H$ or an active derivative thereof. Active derivatives of acids include anhydrides, esters and halides.

5

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether
 10 such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around $-30^\circ C$ to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethylaminopyridine, or a cyclic amine, such as N-methylmorpholine.

15

Where an acid $R^6(CH_2)_tCO_2H$ is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a
 20 N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to reaction with the amine of formula (2).

25

Esters of formula (2) in which R^5 is a $-N(R^7)CS(CH_2)_tR^6$ group may be prepared by treating a corresponding ester in which R^5 is a $-N(R^7)CO(CH_2)_tR^6$ group with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux
 30 temperature.

This reaction may not be particularly suitable with starting materials in which other carbonyl groups are present, for example in L^1 and/or R^6 , and which might undesirably participate in the reaction. To avoid this the reaction with the thiation reagent may be performed earlier in the synthesis of the compound of the invention with an intermediate in which other carbonyl groups are absent and any required carbonyl groups then subsequently introduced by for example acylation as generally described hereinafter.

10

The amines of formula (3) may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2) where appropriate functional groups exist in these compounds. Additionally, although many of the acid intermediates $R^6(CH_2)_tCO_2H$ for use in the coupling reaction described above are known, other desired acids can be derived therefrom using these standard synthetic methods.

Thus, for example compounds of formulae (1), (2) and (3) and acids $R^6(CH_2)_tCO_2H$ may be prepared by alkylation, arylation or heteroarylation. For example compounds containing a L^1H or L^4H group may be alkylated or arylated using a reagent $R^1(Alk^1)_rX$, or $R^{10}(Alk^3)_qX$ in which X is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The alkylation or arylation reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as

dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

- In another example, compounds of formulae (1), (2) and (3) containing a
- 5 L¹H group (where L¹ is for example a -NH- group) and acids R⁶(CH₂)_iCO₂H may be functionalised by acylation or thioacylation, for example by reaction with a reagent R¹(Alk¹)_rL¹X, [wherein L¹ is a -C(O)-, -C(S)-, -N(R⁸)C(O) or -N(R⁸)C(S)- group], R¹⁰(Alk³)_qCOX or R¹⁰(Alk³)_qNHCOX in the presence of a base, such as a hydride, e.g.
- 10 sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature, or by reaction with R¹(Alk¹)_rCO₂H or R¹⁰(Alk³)_qCO₂H or an activated derivative thereof, for example as
- 15 described above for the preparation of esters of formula (2).

- In a further example a compound may be obtained by sulphonylation of a compound where R¹(Alk¹)_r(L¹)_s is an -OH group by reaction with a reagent R¹(Alk¹)_rL¹Hal [in which L¹ is -S(O)- or -SO₂- and Hal is a halogen atom
- 20 such as a chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

- 25 In another example, a compound where R¹(Alk¹)_r(L¹)_s is a -L¹H group, may be coupled with a reagent R¹OH (where R¹ is other than a hydrogen atom) or R¹Alk¹OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate to yield a compound containing a
- 30 R¹(Alk¹)_rO- group.

- In a further example, ester groups -CO₂Alk⁵ in the compounds may be converted to the corresponding acid [-CO₂H] by acid- or base-catalysed hydrolysis depending on the nature of the group Alk⁵ using the reactants
- 35 and conditions described above for the hydrolysis of esters of formula (2).

In another example, $-OR^{12}$ groups [where R^{12} represents an alkyl group such as methyl group] in compounds of formulae (1) or (2) may be cleaved to the corresponding alcohol $-OH$ by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around $-78^{\circ}C$.

Alcohol $[-OH]$ groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{12}$ group (where R^{12} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, $-OH$ groups may be generated from the corresponding ester $[-CO_2Alk^5]$ or aldehyde $[-CHO]$ by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

Aminosulphonylamino $[-NHSO_2NH_2]$ groups in the compounds may be obtained, in another example, by reaction of a corresponding amine $[-NH_2]$ with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine $(-NH_2)$ groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine $[-NH_2]$ groups in compounds of formulae (1) or (2) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro $[-NO_2]$ group may be reduced to an amine $[-NH_2]$, for example by catalytic hydrogenation using for example hydrogen

in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

5

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

10

15 In another example, sulphur atoms in the compounds, for example when present in a linker group L¹ or L³ may be oxidised to the corresponding sulfoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

20

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively
25 by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

30

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

35

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers
5 may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated
10 using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

The following Examples illustrate the invention. All temperatures are in
15 °C. The following abbreviations are used:

EDC - 1-(3-dimethylaminopropyl)3-ethylcarbodiimide;	DMSO - dimethylsulphoxide;
DMF - dimethylformamide;	THF - tetrahydrofuran;
HOBT - 1-hydroxybenzotriazole;	NMM - N-methylmorpholine;
TFA - trifluoroacetic acid;	Ph - phenyl;
20 DCM - dichloromethane;	EtOAc - ethyl acetate;
BOC - <u>tert</u> -butoxycarbonyl;	LDA - lithium diisopropylamide
MeOH - methanol;	Ar - aryl;
tyr - tyrosine;	pyr - pyridine;
HetAr - heteroaryl;	Bu - butyl
25 thiopro - thioproline;	
Me - methyl	

INTERMEDIATE 1

3-Nitro-DL-phenylalanine ethyl ester

30 LDA (2M in heptane/THF/ethyl benzene, 25.45ml, 50.9mmol) was added dropwise to a solution of ethyl N-(diphenylmethylene)glycinate (13g, 48.5mmol) in THF (200ml) at -78°. After 40min a solution of 3-nitrobenzyl bromide (10g, 46.3mmol) in THF (40ml) was added dropwise. The mixture was stirred for 2h and then partitioned between EtOAc (100ml) and water
35 (100ml). The aqueous layer was separated and extracted with EtOAc (2 x 50ml) and the combined organics dried (Na₂SO₄) and evaporated in

vacuo. The residue was then dissolved in ethanol (200ml) and hydrochloric acid (1M, 50ml) was added and the mixture stirred for 0.25h. The volatiles were then removed *in vacuo* and the residue purified by chromatography (SiO₂, Et₂O) to give the title compound as an orange oil (10.0g, 96%). δ H (CDCl₃) 8.09-8.06 (2H, m, Ar), 7.56-7.53 (1H, m, ArH), 7.48-7.43 (1H, m, ArH), 4.15 (2H, q, \downarrow 7.2, OCH₂CH₃), 3.71 (1H, dd, \downarrow 7.8, 5.5Hz, CHCH₂), 3.14 (1H, dd, \downarrow 13.7, 5.5Hz, CHCH_AH_B) 2.95 (1H, dd, \downarrow 13.7, 7.8Hz, CHCH_AH_B), 1.51 (2H, br s, NH₂) and 1.23 (3H, t, \downarrow 7.2, OCH₂CH₃); m/z (ESI, 60V) 239 (M^+ + 1).

10

INTERMEDIATE 2

a) N-Acetyl-D-thiopropine-(3-nitro)-DL-phenylalanine ethyl ester

To a solution of Intermediate 1 (5.3g, 22.3mmol) and N-acetyl-D-thiopropine (3.9g, 22.3mmol) in DCM (100ml) was added NMM (2.67ml, 24.4mmol) HOBT (3.15g, 23.3mmol) and EDC (4.51g, 23.3mmol). The mixture was stirred at room temperature overnight. The solution was then diluted with DCM (100ml) and washed with aqueous HCl (1M, 75ml), saturated aqueous NaHCO₃ (75ml), water (75ml) and brine (75ml), dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂, DCM/MeOH, 97:3) to give the title compound as a viscous oil which solidified on standing (7.25g, 82%). δ H (CDCl₃) 8.10-8.08 (1H, m, ArH), 7.9-7.96 (1H, m, ArH), 7.50-7.42 (2H, m, ArH), 7.28-7.13 (1H, m, NH), 5.02-4.02 (1H, m), and 4.81-4.77 (1H, m) and 4.58-4.43 (2H, m) together (4H, 2xCH α + NCH₂S), 4.22-4.14 (2H, m, OCH₂CH₃), 3.52-3.03 (4H, m, CH₂Ar + CHCH₂S), 2.15 (s) and 2.13 (s) together (3H, CH₃CO) and 1.29-1.23 (3H, m, OCH₂CH₃); m/z (ESI, 60V) 396 (M^+ + 1).

20
25

The following compound was prepared in a similar manner:

b) N-Acetyl-L-thiopropine-D,L-tyrosine methyl ester

from N-acetyl-L-thiopropine and methyl D,L-meta tyrosine. The crude product was chromatographed (silica; EtOAc) to afford the title compound as a white foam (3.5g). δ H (CDCl₃) (approximately a 1:1 mixture of diastereoisomers and 1.5:1 ratio of rotamers) 7.13-7.04 (1H, m), 6.70-6.60 (3H, m), 4.89-4.61 (4H, br m), 4.52 and 4.41 (1H, d's, \downarrow 14Hz), , 3.72, 3.70 and 3.68 (3H, s's), 3.44-2.84 (4H, br m's), 2.16, 2.15, 1.89 and 1.84 (3H, s's); m/z (ES+, 60V) 353 (MH⁺).

35

INTERMEDIATE 3**(O-2,6-Dichlorobenzyl)-DL-m-tyrosine methyl ester**

Sodium hydride (60% dispersion, 0.27g, 6.7mmol) was added to a solution of DL-m-tyrosine methyl ester (1.18g, 6.1mmol) and 2,6-dichlorobenzyl bromide (1.45g, 6.0mmol) in DMF (30ml) at 0°. The reaction was stirred for 2.5h at room temperature then quenched with water (5ml) and the solvent evaporated *in vacuo*. The residue was partitioned between EtOAc (100ml), and water (50ml). The organic layer was washed with water (2 x 50ml), dried (MgSO₄) and the solvent evaporated *in vacuo*. Chromatography (SiO₂ EtOAc/Hexane 4:1) gave the title compound as a gum (1.39g, 65%). δ H (CDCl₃); 7.38-7.21 (4H, m), 6.93-6.82 (3H, m), 5.26 (2H, s), 3.77-3.72 (1H, m), 3.72 (3H, s) and 2.83 (1H, dd, J 8.0, 13.5Hz); m/z (ESI, 60V). 354 ($M^+ + 1$).

EXAMPLE 1**N-Acetyl-D-thiopropine-(3-amino)-DL-phenylalanine ethyl ester**

A solution of Intermediate 2a) (2.00g, 5.06 mmol) and tin (II) chloride dihydrate (5.72g, 25.32mmol) in ethanol (24ml) was stirred at room temperature for 24h. The ethanol was then removed *in vacuo* and the residue partitioned between DCM (10ml) and saturated aqueous Na₂CO₃ (100ml). The solid precipitate formed was removed by filtration and the phases separated. The aqueous phase was extracted with DCM (2 x 50ml) and the combined organics dried (Na₂SO₄) and evaporated *in vacuo* to leave the title compound as a cream foam (1.70g, 95%). δ H (CDCl₃) 7.12-6.80 (2H, m) and 6.72-6.32 (3H, m) together (5H, 4 x ArH + NH), 5.08-4.98 (1H, m), and 4.77-4.36 (3H, m), together (4H, 2 x CH α + NCH₂S), 4.20-4.07 (2H, m, OCH₂CH₃), 3.44-2.89 (4H, m, CH₂Ar + CHCH₂S), 2.01 (s) and 2.06 (s) and 2.08 (2) and 2.14 (s) together (3H, CH₃CO) and 1.27-1.21 (3H, m, OCH₂CH₃); m/z (ESI, 60V) 366 ($M^+ + 1$).

EXAMPLE 2**a) N-Acetyl-D-thiopropine-3-[(2,6-dichloroisonicotinoyl)amino]-DL-phenylalanine ethyl ester**

To a solution of the compound of Example 1 (500mg, 1.36mmol) and NMM (0.166 μ l, 1.50mmol) in DCM (20ml) was added a solution of 2,6-

dichloroisonicotinoyl chloride (316mg, 1.50mmol) in DCM (2ml). The solution was stirred for 2h at room temperature. The reaction mixture was then diluted with DCM (50ml) and washed with water (2 x 25ml) and brine (25ml) dried and evaporated *in vacuo*. The residue was purified by chromatography (SiO₂, DCM/MeOH, 95:5) to give the title compound as a light brown foam (400mg, 56%). δ H (CDCl₃) 9.51 (s) and 9.22 (s) and 8.97 (s) and 8.81 (s) together (1H, NH), 8.50 (2H, s, 2 x ArCl₂H), 7.91-7.84 (1H, m, ArH), 7.27-7.22 (1H, m, ArH), 7.08-7.11 (1H, m, NH), 6.84-6.89 (1H, m, ArH), 6.72-6.77 (1H, m, ArH), 5.06-4.42 (4H, m, 2 x CH α + NCH₂S), 4.23-4.11 (2H, m, OCH₂CH₃), 3.36-3.00 (4H, m, CH₂Ar + CHCH₂S), 2.06 (s) and 2.01 (s) and 1.91 (s) and 1.88 (s) together (3H, CH₃CO) and 1.32-1.23 (3H, m, OCH₂CH₃); m/z (ESI, 60V) 539 (M^+ + 1).

The following compound was prepared in a similar manner:

b) **N-Acetyl-D-thiopropine-3-[(4-methoxyphenylacetyl)amino]-DL-phenylalanine ethyl ester**

from the compound of Example 1 and 4-methoxyphenylacetyl chloride to yield the title compound as a white foam. δ H (CDCl₃) (mixture of rotameric and diastereomeric species) 8.06 (s) and 8.00 (s) together (1H, CONH), 7.67 (1H, t, J 8.3Hz, CONH), 7.3-6.7 (8H, m, ArH), 5.10 (dd) and 4.95 (dd, J 7.0, 3.7Hz) and 4.8-4.3 (m) together (4H, 2 x CH α + NCH₂S), 4.2-4.1 (2H, m, CO₂CH₂CH₃), 3.80 (3H, s, OMe), 3.64 (s) and 3.62 (s) together (2H, COCH₂Ar), 3.4-3.0 (4H, m, CHCH₂Ar + CHCH₂S), 2.11 (s) and 2.07 (s) together (3H, NCOCH₃), 1.29-1.22 (3H, m, CO₂CH₂CH₃) and 1.29-1.22 (3H, m, CO₂CH₂CH₃); m/z (ES⁺, 60V) 514 (M^+ + H).

EXAMPLE 3

a) **N-Acetyl-D-thiopropine-3-[(2,6-dichloroisonicotinoyl)amino]-DL-phenylalanine**

The compound of Example 2a) (400mg, 0.74mmol) was dissolved in a mixture of THF (5ml) and water (5ml). Lithium hydroxide monohydrate (34mg, 0.82mmol) was added and the mixture stirred at room temperature for 2h. The THF was removed under reduced pressure and the aqueous residue acidified with aqueous HCl (1M, 2ml) and the precipitate formed extracted into DCM/MeOH (20ml, 95:5). The organics were separated, dried and evaporated *in vacuo*. The solid obtained was dried under

reduced pressure at 50° to give the title compound (230mg, 61%), δ H (DMSO- d_6 , 400K) 10.36 (1H, br s, NH), 8.69 (2H, s, 2 x ArCl₂H), 7.75-7.63 (1H, m, NH), 7.50 (2H, br s, 2 x ArH), 7.27 (1H, dd, J 8.5, 7.5Hz, ArH), 7.05 (1H, d, J 7.5Hz, ArH), 4.83-4.73 (2H, m) and 4.62-4.52 (1H, m) and
 5 4.38-4.34 (1H, m) together 4H, 2 x CH α + NCH₂S, 3.321-2.95 (4H, m, CH₂Ar + CHCH₂S), and 1.99 (s) and 1.95 (s) together (3H, CH₃CO); m/z (ESI, 60V) 512 (M^+ +1).

The following compound was prepared in a similar manner:

10 **b) N-Acetyl-D-thioproline-3-[(4-methoxyphenylacetyl)amino]-DL-phenylalanine**

from the compound of Example 2b) to yield the title compound as a pale cream powder. δ H (DMSO- d_6) (mixture of rotameric and diastereomeric species) 10.02 (s) and 10.00 (s) together (1H, CONH), 8.47 (d, J 8.0Hz and 8.19 (d, J 8.5Hz) together (1H, CONH), 7.49 - 7.39 (2H, m, ArH), 7.25 - 7.16 (3H, m, ArH), 6.91 - 6.86 (3H, m, ArH), 4.79-4.66 (2H, m), and 4.44-4.18 (2H, m), together (2 x CH α + NCH₂S), 3.73 (3H, s, OMe), 3.54 (2H, s, COCH₂Ar), 3.17-2.74 (4H, m, CHCH₂Ar + CHCH₂S), 2.04 (s) and 1.83 (s) together (3H, COCH₃); m/z (ES⁺, 60V) 486 (M^+ + H).

20

EXAMPLE 4

N-Acetyl-D-thioproline-3[2,6-dichlorophenylacetyl]amino]-DL-phenylalanine ethyl ester

To a solution the compound of Example 1 (500mg, 1.36mmol) and NMM (166 μ l, 1.50mmol) in DCM (20ml) was added a solution of 2,6-dichlorophenylacetyl chloride (335mg, 1.50mmol) in DCM (2ml). The solution was stirred for 2h at room temperature overnight. The reaction mixture was then diluted with DCM (50ml) and washed with aqueous HCl (1M, 25ml), water (25ml) and brine (25ml), dried and evaporated *in vacuo*. The
 25 residue was purified by chromatography (SiO₂, DCM/MeOH, 94:6) to give the title compound as a pale yellow solid (750mg, 100%). δ H (CDCl₃) 8.49 (s) and 8.44 (s) together (1H, NH), 7.67-6.78 (8H, m, 7 x ArH + NH), 5.07-4.38 (4H, m, 2 x CH α + NCH₂S), 4.16-3.99 (4H, m, OCH₂CH₃ + COCH₂Ar), 3.36-2.96 (4H, m, CH₂Ar + CHCH₂S), 2.10 (s) and 2.01 (s) and 1.91 (s) together (3H, CH₃CO) and 1.25-1.21 (3H, m, OCH₂CH₃); m/z
 30 and 1.91 (s) together (3H, CH₃CO) and 1.25-1.21 (3H, m, OCH₂CH₃); m/z (ESI, 60V) 554 (M^+ + 1).

EXAMPLE 5**N-Acetyl-D-thiopropine-3-[(2,6-dichlorophenylacetyl)amino]-DL-phenylalanine**

- 5 The compound of Example 4 (750mg, 1.37mmol) was dissolved in a mixture of THF (10ml) and water (10ml). Lithium hydroxide monohydrate (63mg, 1.49mmol) was added and the mixture stirred at room temperature for 1.5h. The THF was removed under reduced pressure and the aqueous residue acidified with aqueous HCl (1M) and the precipitate formed
- 10 isolated by filtration and washed with water. The solid was recrystallised from acetonitrile to give the title compound as a white solid (290mg, 41%). δ H (DMSO- d_6 , 390K) 9.68 (1H, br s, NH), 7.78-7.66 (1H, m, NH), 7.45-7.39 (4H, m, 4 x ArH), 7.30 (1H, dd, \downarrow 8.9, 7.2Hz, ArH), 7.18 (1H, dd, \downarrow 7.9, 7.6Hz, ArH), 6.93 (1H, br d, \downarrow 7.6Hz, ArH), 4.82-4.71 (2H, m) and 4.57-
- 15 4.47 (1H, m) and 4.37-4.34 (1H, m) together (4H, 2 x CH α + NCH $_2$ S), 4.07 (2H, s, COCH $_2$ Ar), 3.30-2.90 (4H, m, CH $_2$ Ar + CHCH $_2$ S) and 1.98 (s) and 1.95 (s) together (3H, CH $_3$ CO); m/z (ESI, 60V) 525 (M^+ + 1).

EXAMPLE 6

- 20 **2-Chloronicotinoyl-(O-2,6-dichlorobenzyl)-DL-m-tyrosine methyl ester**
EDC (0.30g, 1.57mmol) was added to a suspension of Intermediate 3 (0.51g, 1.43mmol), 2-chloronicotinic acid (0.23g, 1.43mmol), NMM (0.36ml, 3.15mmol) and HOBt (0.36g, 1.50mmol) in DMF (20ml). The reaction was stirred for 16h at room temperature then water (5ml) was
- 25 added and the mixture evaporated *in vacuo*. The residue was partitioned between EtOAc (50ml) and water (50ml). The organic layer was washed with water (50ml), dried (MgSO $_4$) and the solvent removed *in vacuo*. Chromatography (SiO $_2$ EtOAc/Hexane 7:3) gave the title compound as a foam (0.509g, 72%). δ H (CDCl $_3$) 8.45 (1H, dd, \downarrow 2.0, 4.8Hz), 8.06 (1H,
- 30 dd, \downarrow 2.0, 7.6Hz), 7.37-7.21 (4H, m), 7.0-6.79 (4H, m), 5.23 (2H, s), 5.08 (1H, dd, \downarrow 5.8, 13.2Hz), 3.79 (3H, s) and 3.27 (2H, dd, \downarrow 6.0, 13.9Hz); m/z (ESI, 60V) 493 (M^+).

EXAMPLE 7

- 35 **N-Acetyl-D-thiopropine-(O-2,6-dichlorobenzyl)-DL-m-tyrosine methyl ester**

EDC (0.53g, 2.75mmol) was added to a suspension of Intermediate 3 (0.88g, 2.5mmol), NMM (0.61ml, 5.5mmol), and N-acetyl-D-thiopropine (0.44g, 2.5mmol) in DMF (20ml). The reaction was stirred at room temperature for 16h, then water (5ml) was added and the solvent evaporated *in vacuo*. The residue was partitioned between EtOAc (50ml) and water (20ml). The organic layer was washed with water (20ml), dried (MgSO₄) and the solvent removed *in vacuo*. Chromatography (SiO₂, EtOAc/hexane 70:30) gave two diastereoisomers A (0.52g, 40%) and B (0.52g, 40%) as foams.

- 10 (A) δ H (CDCl₃) 7.43-6.75 (7H, m), 5.24 (2H, s), 5.04-3.01 (8H, m), 3.75 (3H, s) and 2.06-1.86 (3H, m). m/z (ESI, 60V) 511 (MH⁺).
(B) δ H (CDCl₃) 7.38 (7H, m), 5.25 (2H, d, \downarrow 3.4Hz), 5.04-3.09 (8H, m), 3.75 (3H, s) and 2.14-1.75 (3H, m). m/z (ESI, 60V) 511 (MH⁺).

15 **EXAMPLE 8**

2-Chloronicotinoyl-(O-2,6-dichlorobenzyl)-DL-m-tyrosine

- A solution of the compound of Example 6 (0.50g, 1.0mmol) in THF (10ml) and water 10ml), was treated with lithium hydroxide monohydrate (65mg, 1.5mmol) and stirred at room temperature for 1h. The THF was evaporated *in vacuo* and the mixture acidified to pH 7 with dilute aqueous HCl, then purified by ion exchange chromatography (Dowex 50 x 4-400, CH₃CN/water) to give the title compound as a white solid (0.40g, 80%).
20 δ H (CD₃OD); 10.41 (1H, d, \downarrow 8.1Hz), 9.93 (1H, dd, \downarrow 1.8, 4.8Hz), 9.14-8.40 (8H, m), 6.69 (2H, s), 6.13 (1H, m), 5.51 (1H, br s) and 4.69-4.37 (2H, m).
25 m/z (ESI, 60V) 481 (M⁺).

EXAMPLE 9

N-Acetyl-D-thiopropine-(O-2,6-dichlorobenzyl)-m-tyrosine

- A solution of the compound of Example 7, Isomer A (0.51g, 1.0mmol) in THF (10ml) and water (10ml) was treated with lithium hydroxide monohydrate (64mg, 1.5mmol) and stirred at room temperature for 1h. The THF was evaporated *in vacuo* and then the mixture was acidified to pH 7 with dilute aqueous HCl. The mixture was purified by ion exchange chromatography (Dowex resin 50 x 4-400, MeCN) to give the title compound as a white solid (0.243g, 47%).
30 δ H (DMSO 390K); 7.52-7.39 (3H, m), 7.23-7.18 (1H, m), 6.93-6.85 (3H, m), 5.27 (2H, s), 4.80-4.71 (2H, m), 4.51-4.41 (2H, m), 4.21-4.11 (2H, m), 3.91-3.81 (2H, m), 3.61-3.51 (2H, m), 3.31-3.21 (2H, m), 3.01-2.91 (2H, m), 2.71-2.61 (2H, m), 2.41-2.31 (2H, m), 2.11-2.01 (2H, m), 1.91-1.81 (2H, m), 1.61-1.51 (2H, m), 1.41-1.31 (2H, m), 1.21-1.11 (2H, m), 1.01-0.91 (2H, m), 0.81-0.71 (2H, m), 0.61-0.51 (2H, m), 0.41-0.31 (2H, m), 0.21-0.11 (2H, m), 0.01 (3H, s).
35 m/z (ESI, 60V) 481 (M⁺).

m), 4.62-4.56 (1H, m), 4.33 (1H, d, \downarrow 9.2Hz), 3.3-2.48 (4H, m) and 1.93 (3H, s). m/z (ESI, 60V), 497 (MH⁺).

EXAMPLE 10

N-Acetyl-D-thiopropine-(O-2,6-dichlorobenzyl)-m-tyrosine

- 5 A solution of the compound of Example 7, isomer B (0.51g, 1.0mmol) in THF (10ml) and water (10ml), was treated with lithium hydroxide monohydrate (64mg, 1.5mmol) and stirred at room temperature for 1h. The THF was evaporated *in vacuo* and the mixture acidified to pH 7 with dilute aqueous HCl, the aqueous was then passed through a Dowex resin
- 10 column 50 x 40. The mixture was purified by ion exchange chromatography (Dowex resin 50 x 4-400, MeCN) to give the title compound as a white solid (0.37g, 63%). δ H (DMSO 390K) 7.52-7.39 (3H, m), 7.2 (1H, m), 6.92-6.85 (3H, m), 5.27 (2H, s), 4.80-4.71 (2H, m), 4.58-4.53 (1H, m), 4.35 (1H, d, \downarrow 8.9Hz), 3.26-3.11 (2H, m), 3.0-2.92 (2H,
- 15 m) and 1.93 (3H, s). m/z (ESI, 60V), 497 (M⁺).

EXAMPLE 11

N-Acetyl-D-thiopropine-3-[(trimethylacetyl)amino]-DL-phenylalanine ethyl ester

- 20 Trimethylacetyl chloride (168 μ l, 1.36mmol) was added to a solution of the compound of Example 1 (450mg, 1.23mmol) and NMM (148 μ l, 1.36mmol) in DCM (30ml). The reaction mixture was stirred for 5h at room temperature then diluted with DCM (50ml), washed with dilute HCl(aq) (25ml), water (2 x 25ml) and brine (25ml), dried and evaporated *in vacuo*.
- 25 The residue was purified by column chromatography [SiO₂, DCM/MeOH, 97:3] to give the title compound as a white foam (460mg, 83%). δ H (CDCl₃) (mixture of rotameric and diastereomeric species observed) 8.20 (s) and 8.10 (s) together (1H, NH), 7.85 (1H, apparent t, \downarrow 9.4Hz, NH), 7.5-6.5 (4H, m, ArH), 5.2-4.1 (6H, m, 2 x CH α , NCH₂S, CO₂CH₂CH₃), 3.5-3.0
- 30 (4H, m, CH₂Ar + CHCH₂S), 1.7 (s) and 2.15 (s) together (3H, NCOCH₃), 1.32-1.22 (12H, m, CH₃CO + CO₂CH₂CH₃); m/z (ES⁺, 60V) 450 (M⁺ + 1).

EXAMPLE 12

N-Acetyl-D-thiopropine-3-[(trimethylacetyl)amino]-DL-phenylalanine

- 35 The title compound was obtained as a white powder by hydrolysis of the ester of Example 11 using the procedure of Example 3a). δ H (DMSO-d₆)

(mixture of rotameric + diastereomeric species) 9.09 (1H, br s, NH), 8.46 (t, \downarrow 8.9Hz), 8.20 (d, \downarrow 8.2Hz) and 8.09 (d, \downarrow 7.7Hz), together (1H, H), 7.58-7.4 (2H, m, ArH), 7.19-7.12 (1H, m, ArH), 6.92-6.87 (1H, m, ArH); 4.86-4.64 (2H, m) and 4.47-4.19 (2H, m) together (2 x CH α + NCH $_2$ S), 3.38-2.80 (4H, m, CH $_2$ Ar + CHCH $_2$ S), 2.08 (s), 2.07 (s), 1.85 (s) and 1.78 (s) together (3H, NCOCH $_3$) and 1.22 (9H, s, Me $_3$ CO); m/z (ES $^+$, 60V) 422 (M $^+$ +H).

EXAMPLE 13

10 N-Acetyl-L-thiopropine-D,L-O-(1-adamantanecarbonylmethyl)-m-tyrosine methyl ester

A mixture of Intermediate 2b) (1.0g, 2.84mmol), caesium carbonate (0.926g, 2.84mmol) and 1-adamantylbromomethylketone (0.73g, 2.84mmol) in dry DMF (30ml) was stirred at room temperature for 2h. The
15 volatiles were removed *in vacuo* and the residue partitioned between EtOAc (100ml) and 2% aqueous HCl (40ml). The phases were separated and the aqueous phase re-extracted with EtOAc (2 x 30ml). The combined organic extracts were washed with brine (10ml), dried (MgSO $_4$) and evaporated *in vacuo* to afford a colourless foam. Purification by
20 chromatography (silica; EtOAc) afforded the title compound as a colourless foam (824mg, 55%). δ H (CDCl $_3$) (approximately a 1:1 mixture of diastereoisomers and 1.5:1 ratio of rotamers) 7.21-7.14 (1H, m), 6.84-6.71 (3H, m), 5.01-4.96 (2H, m), 4.93-4.62 (4H, m's), 4.53 and 4.40 (1H, d's, \downarrow 14Hz), 3.74, 3.72 and 3.70 (3H, s's), 3.42-2.83 (4H, br m) and 2.1-
25 1.72 (18H, m's and s's); m/z (ES $^+$, 60V) 551 (MNa $^+$) and 529 (MH $^+$).

EXAMPLE 14

N-Acetyl-L-thiopropine-D,L-O-(1-adamantanecarbonylmethyl)-m-tyrosine

30 The compound of Example 13 (258mg, 0.49mmol) was treated with a solution of LiOH.H $_2$ O (23mg, 0.55mmol) in water (2.5ml) and dioxane (2.5ml) at room temperature for 2h. The reaction mixture was acidified with a few drops of concentrated HCl and the volatiles removed *in vacuo*. The residue was chromatographed [silica; DCM (200), MeOH (20), AcOH
35 (3), H $_2$ O (2)] to afford the product as a colourless oil. Freeze drying from aqueous methanol gave the title compound as a white amorphous solid

(240mg, 96%). δ H (CDCl₃) (approximately 1:1 mixture of diastereoisomers and 1.5:1 ratio of rotamers) 7.21-7.12 (1H, m, apparent t), 6.88-6.70 (3H, m), 5.0-4.96 (2H, m), 4.90-4.61 (3H, br m), 4.54 and 4.40 (1H, d, Δ 14Hz), 3.42-2.85 (4H, m's), 2.12, 2.10, 1.90 and 1.85 (3H, s's), 2.10-2.00 (3H, narrow m) 1.98-1.90 (6H, narrow m) and 1.80-1.76 (6H, narrow m); m/z (ES⁺, 60V) 537 (MNa⁺), 515 (MH⁺).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

15

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with F(ab)₂ fragment goat anti-human IgG Fc γ -specific antibody [Jackson Immuno Research 109-006-098: 100 μ l at 2 μ g/ml in 0.1M NaHCO₃, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 μ l containing 2.5 x 10⁵ Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100 μ l methanol for 10 minutes followed by another wash. 100 μ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100 μ l 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β -lympho blastoid cell-line JY was used in place of Jurkat cells. The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 μ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100 μ l PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200 μ l containing 2.5x 10⁵ K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10⁵ freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 μ l in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100 μ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H₂O₂ (Sigma) and 50 μ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

α_{IIb}/β_3 -dependent human platelet aggregation

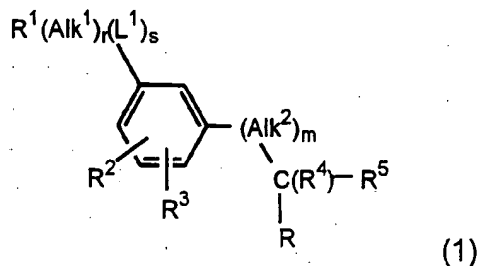
Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich

plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6×10^8 /ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $\text{MgCl}_2 \cdot \text{H}_2\text{O}$ 0.427; CaCl_2 0.2; KCl 0.2; D-glucose 1.0; NaHCO_3 1.0; $\text{NaHPO}_4 \cdot 2\text{H}_2\text{O}$ 0.065). Aggregation was monitored following addition of $2.5 \mu\text{M}$ ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the compounds of the invention, for example compounds of the Examples generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of $1 \mu\text{M}$ and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of $50 \mu\text{M}$ and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

CLAIMS

1. A compound of formula (1):



wherein

10 R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;

L^1 is a linker atom or group;

r and s is each zero or an integer 1;

15 R^2 and R^3 , which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

20 R^4 is a hydrogen atom or a methyl group;

25 R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

R is a carboxylic acid ($-CO_2H$) or a derivative thereof; and the salts, solvates and hydrates thereof.

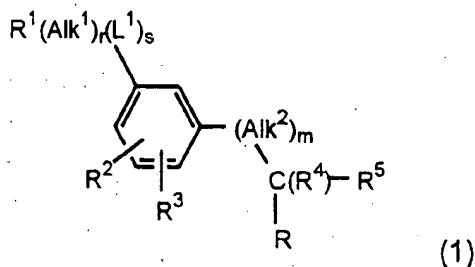
- 30 2. A compound according to Claim 1 wherein R is $-CO_2H$.

3. A compound according to Claim 1 or Claim 2 wherein Alk^2 is $-\text{CH}_2-$ and m is the integer 1.
4. A compound according to Claim 1 to Claim 3 wherein R^4 is a hydrogen atom.
5. A compound according to Claim 1 to Claim 4 wherein $-(\text{Alk}^1)_r(\text{L}^1)_s$ is $-\text{CH}_2\text{O}-$ or $-\text{CON}(\text{R}^8)-$.
6. A compound according to Claim 5 wherein $(\text{Alk}^1)_r(\text{L}^1)_s$ is $-\text{CONH}-$.
7. A compound according to Claim 1 to Claim 6 wherein R^1 is an optionally substituted aromatic or heteroromatic group.
8. A compound according to Claim 7 wherein R^1 is an optionally substituted phenyl, pyridyl or pyrimidinyl group.
9. A compound according to any of the preceding claims wherein R^5 is a group $-\text{L}^2(\text{CH}_2)_t\text{R}^6$ in which R^6 is an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.
10. A compound according to Claim 9 wherein R^6 is an optionally substituted pyrrolidinyl, thiazolidinyl, phenyl or pyridyl group.
11. A compound according to any of the preceding claims wherein R^5 is a $-\text{NHCOR}^6$ or $-\text{NHCSR}^6$ group.
12. A compound which is:
 - N*-Acetyl-*D*-thioproline-3-[(2,6-dichloroisonicotinoyl)amino]-*DL*-phenylalanine;
 - N*-Acetyl-*D*-thioproline-3-[(4-methoxyphenylacetyl)amino]-*DL*-phenylalanine;
 - N*-Acetyl-*D*-thioproline-3-[(2,6-dichlorophenylacetyl)amino]-*DL*-phenylalanine;
 - 2-Chloronicotinoyl-(0-2,6-dichlorobenzyl)-*DL*-*m*-tyrosine;

and the salts, solvates and hydrates thereof.

13. A pharmaceutical composition comprising a compound of formula (1):

5



wherein

- 10 R^1 is a hydrogen atom or an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
- Alk^1 is an optionally substituted aliphatic or heteroaliphatic chain;
- L^1 is a linker atom or group;
- r and s is each zero or an integer 1;
- 15 R^2 and R^3 , which may be the same or different, is each a hydrogen or halogen atom or a straight or branched alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxyl or nitro group;
- Alk^2 is a straight or branched alkylene chain;
- m is zero or an integer 1;
- 20 R^4 is a hydrogen atom or a methyl group;
- R^5 is a group $-L^2(CH_2)_tR^6$ in which L^2 is a $-N(R^7)CO-$ [where R^7 is a hydrogen atom or a straight or branched alkyl group] or $-N(R^7)CS-$ group, t is zero or the integer 1, and R^6 is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic,
- 25 heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;
- R is a carboxylic acid ($-CO_2H$) or a derivative thereof;
- and the salts, solvates and hydrates thereof;
- together with one or more pharmaceutically acceptable carriers,
- 30 excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01615

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/078 C07D213/82 A61K38/05 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 842 945 A (HOECHST AG) 20 May 1998 (1998-05-20) the whole document ---	1,2,4,13
X	EP 0 842 943 A (HOECHST AG) 20 May 1998 (1998-05-20) the whole document ---	1-4,13
X	FU H ET AL: "Preliminary study on synthesis and antitumor activity in vitro of derivatives of timonacic" CHEMICAL ABSTRACTS + INDEXES, vol. 108, no. 17, 25 April 1988 (1988-04-25), XP002114106 ISSN: 0009-2258 abstract no. 150358; see abstract --- -/--	1-4, 9-11,13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

2 September 1999

Date of mailing of the international search report

17.09.1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Groenendijk, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01615

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages.	Relevant to claim No.
X	"N-(4-Thiazolidinyl)carbonyl amino acid derivatives" CHEMICAL ABSTRACTS + INDEXES, vol. 95, no. 19, 9 November 1981 (1981-11-09), XP002114107 ISSN: 0009-2258 abstract no.169173; see abstract ----	1-4, 9-11,13
P,X	WO 99 06434 A (LOMBARDO LOUIS JOHN ;SEMKO CHRISTOPHER M (US); THORSETT EUGENE D ()) 11 February 1999 (1999-02-11) See esp.p. 14, line 41 to page 15, 1.8; p.16, 14-7; examples 32-37,51,52; claims 1-26 ----	1-11,13
P,X	WO 99 10312 A (HOFFMANN LA ROCHE) 4 March 1999 (1999-03-04) See especially claims 1,2,4-34,36-43 ----	1-11,13
P,X	WO 98 58902 A (TANABE SEIYAKU CO ;YAMAGISHI MASAFUMI (JP); TEEGARDEN BRADLEY (US)) 30 December 1998 (1998-12-30) See especially examples 45-47,60,61,66,67,70; Tab 6:R.ex 26; Tab. 8: R.ex. 41,42 ----	1-9,11, 13
P,X	WO 99 06431 A (LOMBARDO LOUIS JOHN ;SEMKO CHRISTOPHER M (US); THORSETT EUGENE D ()) 11 February 1999 (1999-02-11) See esp.examples 109,113 ----	1-5, 9-11,13
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P,X	WO 99 06436 A (LOMBARDO LOUIS JOHN ;SEMKO CHRISTOPHER M (US); THORSETT EUGENE D ()) 11 February 1999 (1999-02-11) the whole document ----	1-4, 9-11,13
E	WO 99 35163 A (ARCHIBALD SARAH CATHERINE ;CELLTECH THERAPEUTICS LTD (GB); WARRELL) 15 July 1999 (1999-07-15) See especially example 38 -----	1-4, 9-11,13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 01615

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
1-11,13 (all partially)

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11,13(all partially)

The scope of the claims 1 and 13 is very broad and speculative. A formula consisting virtually of variables which are moreover at least partially ill-defined (e.g. the use of "linker atom or group", "aliphatic or heteroaliphatic chain", "optionally substituted alkyl group", "(hetero)cycloaliphatic" and "(hetero)aromatic") cannot be considered to be a clear and concise definition of patentable subject-matter (Art.6 PCT).

Furthermore the available experimental data actually only comprise a very small part of the compounds claimed, which part is moreover not evenly distributed over the whole claimed area. Therefore the claims can also not be considered to represent a permissible generalisation which is fairly based on experimental evidence, that is, they are also not adequately supported by the description (Art.6 PCT).

Therefore a meaningful search could not encompass the complete subject-matter of the claims. Consequently the search had been directed to the actually synthesised examples and (closely) related analogs, that is the compounds defined by formula 1 wherein R1(Alk1)r(L1)s, (Alk2)m, R4, R5 and R6 have the meanings defined respectively in the claims 2-5, 7 and 9 and their use (Art.17(2)(a)(ii) and (b) PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01615

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WO 9910312 A	04-03-1999	AU 9262098 A	16-03-1999
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WO 9853814 A	03-12-1998	NONE	
WO 9906436 A	11-02-1999	AU 8585198 A	22-02-1999
WO 9935163 A	15-07-1999	NONE	